Rejections under 35 U.S.C. § 112, second paragraph

Claims 1 and 2 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite in failing to recite a final process step that relates back to the preamble. The Examiner takes a position that a method claim must recite a final step that describes the accomplishment of the goals of the method as stated in the preamble.

Applicants submit that the present claims clearly recite the steps to be performed in a positive, active fashion and include in step (b) the term "amplifying", thus accomplishing the goal stated in the preamble. Thus, the present claims overcome the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103(a)

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over McDonough et al ('849) in view of Pergolizzi et al ('764). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that the Examiner fails to make a *prima facie* case of obviousness of the invention. The Examiner asserts that McDonough et al teach a method for amplifying a DNA by polymerase chain reaction using a DNA fragment comprising a nucleotide analog as a template, characterized in that the

method for amplifying a DNA is carried out in the presence of a compound (DMSO) for lowering the Tm value of a double-stranded nucleic acid and, "McDonough et al teach a method for amplifying a DNA characterized in that the DNA fragment is a cDNA prepared by reverse transcription reaction using an RNA as a template".

The Examiner has not correctly appreciated the McDonough reference. In the method of McDonough, DNA amplification is carried out with a modified oligonucleotide as a primer. There is no mention of a template DNA comprising a nucleotide analog.

In contrast, according to the present invention, a DNA comprising at least one nucleotide analog is used as a template and the template is further amplified in the presence of nucleotide analogs. Thus, a desired DNA is amplified with uniform incorporation of nucleotide analogs regardless of the GC content even in admixture of undesired DNAs. This is completely distinguishable from the method disclosed in McDonough.

In addition, although McDonough teaches amplification using DMSO, the DMSO is simply used as an additive to enhance amplification as described in column 12, lines 21 to 24 in their specification. The DMSO is not used for lowering the Tm value of a double-stranded nucleic acid as taught in the present invention.

Pergolizzi discloses a method of amplification using an analog of guanosine nucleotide to be incorporated in a DNA strand in place of dGTP, However, in the invention of Pergolizzi, the purpose of the use of the above analog is to amplify a GC-rich nucleic acid, not to lower the Tm value of a double-stranded nucleic acid as taught in the present invention.

Also in the invention of Pergolizzi, since the nucleotide analogs used are only those to be incorporated into a DNA strand in place of dGTP, when the GC content is low, only a slight amount of the nucleotide analogs can be incorporated.

On the other hand, as described by the present claims, a nucleotide analog substituting dATP or dTTP is used in addition to an analog substituting dGTP or dCTP. As a result, the nucleotide analogs can be incorporated into a synthetic chain at a uniform frequency without being affected by the GC content of the template. Thus, the present invention is completely distinguishable from the disclosure of Pergolizzi.

The method of the present invention makes it possible to selectively amplify only the target sequence derived from RNA by lowering Tm value without being affected by the GC content. This result is not apparent from McDonough in view of Pergolizzi.

In addition, Pergolizzi teaches only the use of constituents such as DMSO which improve the replication or

transcription of GC rich nucleic acids in the GC rich nucleic acid amplification using an analog of guanosine (see column 8, lines 65 to 68), but not the use of constituents such as DMSO in amplification of nucleic acids that are not GC rich. Therefore an ordinary artisan would never have been motivated to combine the inventions of Pergolizzi and McDonough.

Even if these methods were combined an ordinary artisan would achieve a method for amplifying a desired GC-rich nucleic acid, wherein the nucleic acid is amplified using a DNA as a template and a modified oligonucleotide as a primer in the presence of an analog of guanosine nucleotide and DMSO, the DNA as a template having no nucleotide analogs. This is different from the present invention, wherein a DNA template having no particular compositional bias, but comprising nucleotide analogs, is amplified in the presence of a nucleotide analog that substitutes for dGTP or dCTP and in the presence of a nucleotide analog that substitutes for dATP or dTTP. Thus, even if the references are combined in the manner suggested by the Examiner, one does not arrive at the claimed invention.

Accordingly, the present invention is not *prima facie* obvious in view of McDonough and Pergolizzi, and the instant rejection should be withdrawn.

Claims 1-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over McDonough in view of Pergolizzi as

applied above, and further in view of the Stratagene catalog. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The deficiencies of McDonough and Pergolizzi in asserting *prima facie* obviousness are explained above. The Examiner cites the Stratagene catalog merely for the added teaching that one should combine various reagents into a kit for marketing purposes. This does nothing to remedy the deficiencies of McDonough and Pergolizzi in establishing *prima facie* obviousness of the invention. Accordingly, the rejection of claims 1-16 under 35 U.S.C. § 103(a), over McDonough, Pergolizzi and the Stratagene catalog, should be withdrawn.

Pursuant to the provisions of 37 C.F.R §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of one (1) month to September 30, 2000, in which to file a reply to the Office Action. The required fee of $110.00 is enclosed herewith.

If the Examiner has any questions concerning this application, he is requested to contact Mark Nuell (Reg. No. 36,623) at the telephone number of the undersigned.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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By _____ #36,623

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